Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome

P B Jeppesen,[1] R Gilroy,[2] M Pertkiewicz,[3] J P Allard,[4] B Messing,[5] S J O'Keefe[6]

► Investigators of the Teduglutide 004 Study Group are listed in the online appendix. To view these files please visit the journal online (http://gut.bmj.com).

[1]Department of Gastroenterology CA-2121, Rigshospitalet, Copenhagen, Denmark
[2]Department of Gastroenterology, Kansas University Medical Center, Kansas City, Kansas, USA
[3]Department of General Surgery and Clinical Nutrition, Medical University of Warsaw, Warsaw, Poland
[4]Department of Gastroenterology, University of Toronto, Toronto, Ontario, Canada
[5]Department of Gastroenterology and Nutrition support, Pôle des Maladies de l'Appareil Digestif Hôpital Beaujon, Clichy la Garenne, France
[6]Division of Gastroenterology, University of Pittsburgh, Pennsylvania, USA

Correspondence to
Palle Bekker Jeppesen, Department of Medicine CA-2121, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; bekker@dadlnet.dk

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ABSTRACT

Background and aims Teduglutide, a GLP-2 analogue, may restore intestinal structural and functional integrity by promoting repair and growth of the mucosa and reducing gastric emptying and secretion, thereby increasing fluid and nutrient absorption in patients with short bowel syndrome (SBS). This 24-week placebo-controlled study evaluated the ability of teduglutide to reduce parenteral support in patients with SBS with intestinal failure.

Methods In 83 patients randomised to receive subcutaneous teduglutide 0.10 mg/kg/day (n=32), 0.05 mg/kg/day (n=35) or placebo (n=16) once daily, parenteral fluids were reduced at 4-week intervals if intestinal fluid absorption (48 h urine volumes) increased ≥10%. Responders were subjects who demonstrated reductions of ≥20% in parenteral volumes from baseline at weeks 20 and 24. The primary efficacy end point, a graded response score (GRS), took into account higher levels and earlier onset of response, leading to longer duration of response. The intensity of the response was defined as a reduction from baseline in parenteral volume (from 20% to 100%), and the duration of the response was considered the response at weeks 16, 20 and 24. The results were tested according to a step-down procedure starting with the 0.10 mg/kg/day dose.

Results Using the GRS criteria, teduglutide in a dose of 0.10 mg/kg/day did not have a statistically significant effect compared with placebo (8/32 vs 1/16, p=0.16), while teduglutide in a dose of 0.05 mg/kg/day had a significant effect (16/35, p=0.007). Since parenteral volume reductions were equal (353±475 and 354±334 ml/day), the trend towards higher baseline parenteral volume (1816±1008 vs 1374±639 ml/day, p=0.11) in the 0.10 mg/kg/day group compared with the 0.05 mg/kg/day group may have accounted for this discrepancy. Three teduglutide-treated patients were completely weaned off parenteral support. Serious adverse events were distributed similarly between active treatment groups and placebo. Villus height, plasma citrulline concentration and lean body mass were significantly increased with teduglutide compared with placebo.

Conclusions Teduglutide was safe, well tolerated, intestinotrophic and suggested pro-absorptive effects facilitating reductions in parenteral support in patients with SBS with intestinal failure.

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Significance of this study

What is already known on this subject?

- In an open-label non-placebo controlled 21-day phase 2 study, teduglutide has been shown to increase intestinal wet weight absorption in patients with short bowel syndrome using metabolic balance studies.

What are the new findings?

- This is the first long-term (24 weeks) randomised placebo-controlled study of teduglutide in patients with short bowel syndrome dependent on parenteral support.
- Teduglutide was safe, well tolerated and led to restoration of intestinal functional and structural integrity through significant intestinotrophic and pro-absorptive effects.

How might it impact on clinical practice in the foreseeable future?

- Teduglutide has the potential to reduce the burden often seen with parenteral support in patients with short bowel syndrome with intestinal failure, and could add to the limited clinical treatment armamentarium in treating patients with short bowel syndrome.

INTRODUCTION

Short bowel syndrome (SBS) is characterised by large heterogeneity where patients with intestinal insufficiency are able to compensate for their elements, vitamins or nutrients by increasing oral intake and adapt metabolically,[1 2] whereas patients with intestinal failure depend on parenteral support (fluids, electrolytes or nutrients).[3–5] A large part of this heterogeneity is explained by differences in the anatomy of the remnant bowel.[6 7] Patients with mild intestinal failure with a jejunostomy or ileostomy need approximately 1000 ml of fluid and electrolytes taken over a few hours 3–7 times per week. Patients with SBS with jejunostomies or ileostomies frequently have complications such as dehydration and electrolyte deficiencies due to stomal losses. In severe cases, significant protein and energy malabsorption can occur and may require supplementary hypertonic nutrients and electrolyte infusions administered both daytime and nocturnally. Patients with SBS and intestinal failure who have a preserved colon in continuity often suffer from large amounts of rectal fluid loss, fear of incontinence and the consequences of colonic fermentation such as gaseous distension and flatulence, whereas fluid and electrolyte

these patients do not imminently suffer from dehydration, days off parenteral nutrients are possible. However, on those nights when nutrient infusions are required, both the infusion and the accompanying excessive urine production may disturb the sleep pattern of the patients. In the most severe cases, nocturnal nutrients as well as daytime fluid and electrolytes are required.

Although frequently life-saving in patients with SBS with intestinal failure, the parenteral administration of fluids, electrolytes, trace elements, vitamins and nutrients has been associated with potentially life-threatening complications. Poor catheter care technique, insertion site, tunnel and catheter-related blood stream infections may lead to bacteraemia and even septicaemia, and the presence of a central catheter may lead to central venous thrombosis and even embolism.[5] In addition, parenteral constituents and chronic dehydration may contribute to progressive intestinal failure-associated liver and renal disease and eventually failure.[8 9] Mutually, the symptoms of SBS with intestinal failure and the inconveniences and complications in relation to parenteral support may cause potential restrictions in the lifestyle of these patients and may lead to significant impairment of their quality of life.[10 11]

In the past, the clinical care of patients with SBS has mainly focused on 'making the most of what the SBS patient still had' by optimising remnant intestinal function through dietary interventions, oral rehydration solutions, antidiarrhoeal and antisecretory agents. Furthermore, anastomosis of excluded bowel has been advocated, when it is possible, and experimental surgical procedures have also been employed. Intestinal transplantation is currently only recommended in patients failing parenteral support due to recurrent life-threatening sepsis, loss of venous access and end stage intestinal failure-associated liver disease.[5] Treatments focused on improving the structural and functional integrity of the remaining intestine by so-called intestinal rehabilitation which minimise or eliminate the need for parenteral support are therefore needed.

In recent years hormonal stimulation to augment remnant bowel adaptation has been suggested, with glucagon-like peptide 2 (GLP-2)—a peptide which is secreted from the intestinal L-cells following ingestion of a meal—as a key factor. Repeated administration of GLP-2 promotes the expansion of the intestinal mucosa via the stimulation of crypt cell growth and the reduction of enterocyte apoptosis.[12] Exogenous GLP-2 administration inhibits gastric acid secretion and gastric emptying,[13 14] stimulates intestinal blood flow,[15] increases intestinal barrier function[16] and enhances nutrient and fluid absorption in both preclinical and clinical models.[17] In addition, GLP-2 may decrease bone resorption and it has been suggested as a potential therapy in osteoporosis.[18]

Open uncontrolled clinical studies have suggested positive effects of exogenously administered GLP-2 and the di-peptidyl peptidase IV degradation resistant analogue, teduglutide, in patients with SBS.[19–22] In an open-label 3-week study where the oral intake and parenteral support were intentionally kept constant during 72 h balances, teduglutide reduced faecal wet weight excretions by 711±734 g/day (p=0.001) and increased wet weight absorption by 743±477 g/day causing increases in urine volumes of 555±485 g/day (p<0.001). In addition, faecal energy losses decreased by 808±1453 kJ/day (p=0.04) in relation to teduglutide treatment, but all effects reverted 3 weeks after treatment.[22]

In the present study, the largest randomised placebo-controlled trial ever performed in patients with SBS with intestinal failure, requirements. Secondary end points included the ability to obtain additional days off or eliminate the need for parenteral support in this SBS population with demonstrated intestinal failure. In detail, during 24 weeks of treatment with placebo or teduglutide, adjustments in the parenteral support were performed when the urine volume was increased to a certain threshold. This algorithm-based approach considered the changes in urine volumes to be based on changes in intestinal wet weight absorption. In addition to safety evaluations, DEXA scanning, histological evaluation of bowel morphology in biopsies, plasma citrulline and quality of life questionnaires described changes in body composition, structural intestinal adaptation and quality of life, respectively, in relation to placebo and teduglutide treatment.

METHODS

Patients, study design, efficacy and safety

After receiving approval from local IRBs and medical ethics committees, centres screened patients of both sexes aged ≥18 years with a history of SBS due to intestinal resection and dependent on parenteral support (fluids, electrolytes or nutrients) at least three times per week for a period of at least 12 months prior to the start of the study. Exclusion criteria are shown in box 1.

The basic study design is presented in figure 1.

Parenteral optimisation

To establish that the patients minimally tolerated baseline parenteral support resulted in a urine output of 1.0—2.0 l/day, a period of optimisation was used. The patients were instructed how to perform home collections of their 48 h urine output and

Box 1 Exclusion criteria

- Pregnancy or lactation.
- Body mass index <18 or >27 kg/m^2.
- Active Crohn's disease as evaluated by standard procedures employed by the investigator.
- Radiation enteritis, scleroderma, coeliac disease, refractory or tropical sprue, diabetes.
- Alcohol or drug abuse within the last year.
- Previous use of teduglutide or potential allergies to teduglutide or its constituents.
- Inadequate hepatic function: ALT and AST both >2.0× upper limit of normal (ULN), total bilirubin >1.25× ULN or alkaline phosphatases >2.5× ULN.
- Inadequate renal function: serum creatinine or blood urea nitrogen >1.5× ULN.
- Urine sodium <20 mmol/day.
- Any hospitalisation within 1 month before screening.
- Use of infliximab, growth hormone or growth factors such as native GLP-2 or other biological therapy within the last 12 weeks.
- Use of systemic corticosteroids, methotrexate, cyclosporine, tacrolimus, sirolimus, octreotide, intravenous glutamine or any investigational drug within last 30 days.
- The use of antimotility and antidiarrhoeal agents (loperamide, difenoxylate, codeine and other opiates), H_2-receptor antagonists, proton pump inhibitors, bile sequestering agents, oral glutamine, diuretics and oral rehydration solutions were required to be stable for ≥4 weeks prior to baseline

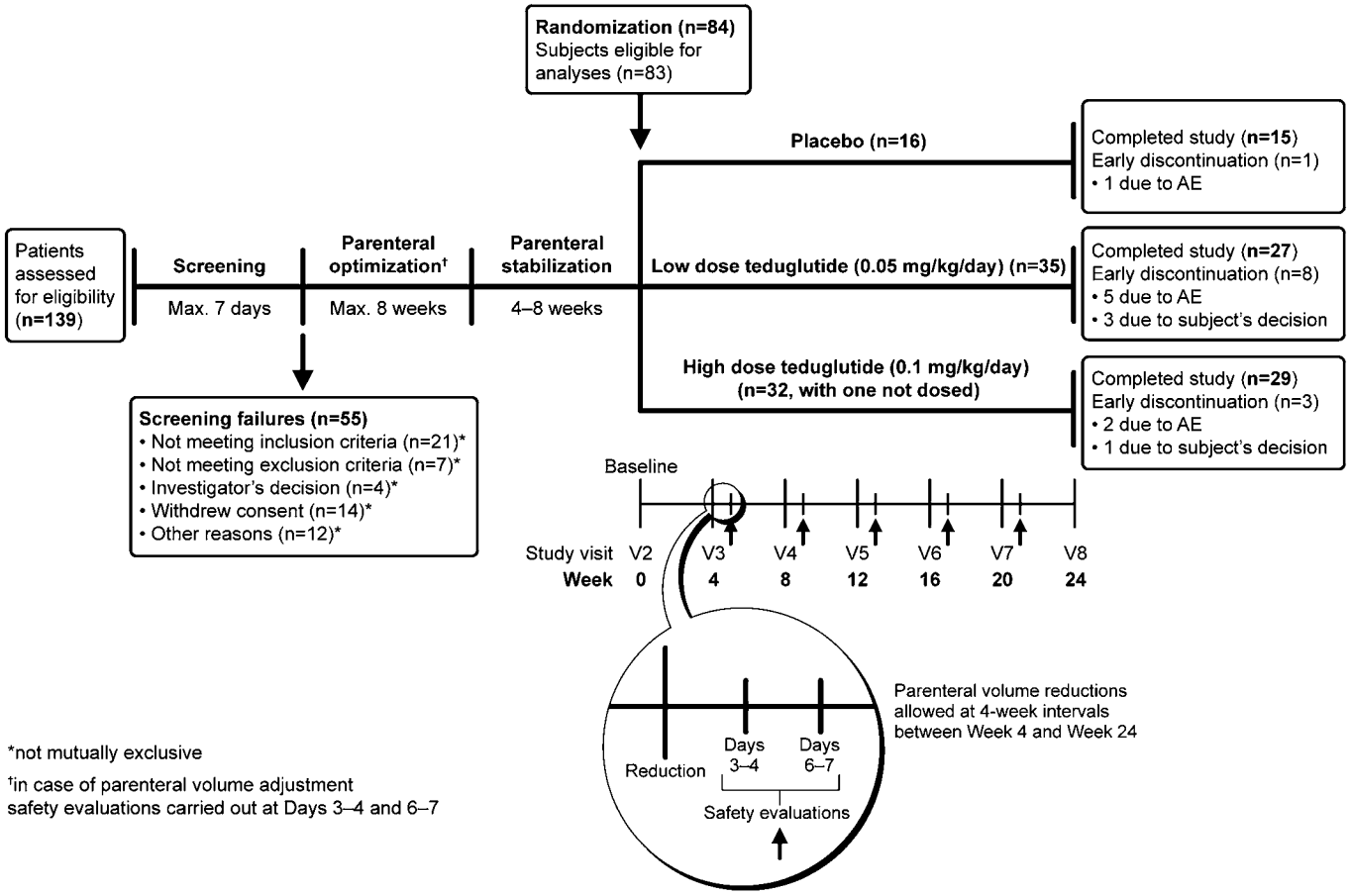


Figure 1 Basic study design. AE, adverse event.

completed these 2 days before each visit. Although the osmolarity and oral intake were not kept strictly controlled, study participants were asked to try to keep the timing, quantity and quality of beverages as constant as possible during the 48 h collection periods. The study subjects were seen in outpatient clinics at 2-week intervals. Adjustment to the study subjects' baseline parenteral volume was performed when urine volume fell below 1.0 l/day or exceeded 2.0 l/day. At all times, interim safety evaluations were performed within 1 week after adjusting parenteral volumes by repeating 48 h urine collections, again recording and keeping oral beverages the same as during previous balances. Blood samples were taken (including haematocrit, blood urea nitrogen and creatinine), urine sodium was measured and a clinical evaluation was performed to check for clinical signs of dehydration. If tolerated, the new parenteral volume was maintained stable until the next visit and, if not, the original parenteral volume was resumed. The patient was excluded from the study if parenteral optimisation was not achieved, defined as stable urine output volume of 1.0–2.0 l/day after 8 weeks.

Parenteral stabilisation

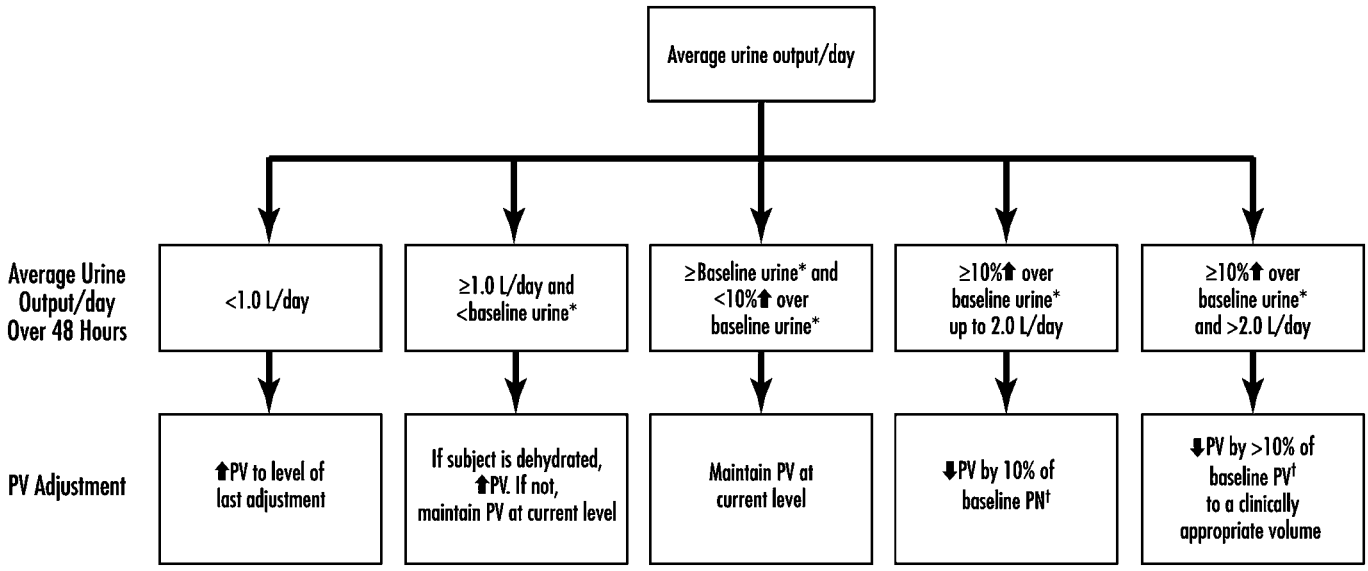
After optimisation, the patients were maintained for 4–8 weeks on the stabilised tolerated parenteral volume. If the patients still had a urine volume of 1.0–2.0 l/day while keeping oral beverages constant, the patients were eligible for randomisation.

Randomisation

Eligible patients were randomly assigned to one of three groups stratified for the three groups and the parenteral volume at three levels of consumption: (1) parenteral volume consisting of intravenous fluids and electrolytes only (3–7 times weekly); (2) parenteral volume consisting of fluids and nutrients 3–5 times weekly; and (3) parenteral volume consisting of fluids and nutrients (6–7 times weekly). These patients with SBS, depending on their parenteral support (nutrients and/or fluids), were randomised to receive teduglutide (Cangene, Winnipeg, Manitoba, Canada) at doses of 0.05 or 0.10 mg/kg/day or placebo (2:2:1) given subcutaneously into one of the four quadrants of the abdomen or either thigh once daily in the morning for 24 weeks. The placebo consisted of a lyophilised powder containing L-histidine, mannitol, monobasic and dibasic sodium phosphate, which were also contained in the active treatment.

Parenteral adjustments after randomisation

A strict parenteral weaning algorithm was used in the protocol that allowed for no more than 10% reductions in parenteral volumes at 4-week intervals (figure 2). Weaning was performed if the 48 h urinary volumes exceeded the baseline values by more than 10%, regardless of the absolute amount. Comparisons for subsequent reductions were always made to baseline urinary volumes. Greater reductions were allowed if urinary volumes exceeded 2.0 l/day. A maximum of five reductions in parenteral support were allowed from baseline to week 24. The physician responsible for adjusting the parenteral support was expert in the management of intestinal failure and parenteral infusion



PV, parenteral volume.

*Baseline urine is the urine volume that was obtained after subjects have demonstrated urine output volume stability for a minimum of 4 weeks following optimisation (a period of optimisation was utilized to establish the patient's minimally tolerated support that resulted in a urine output between 1.0 L/day and 2.0 L/day).

†Baseline PV is the parenteral volume after subjects have demonstrated urine output volume stability for a minimum of 4 weeks following optimisation.

Figure 2 Algorithm for parenteral volume adjustment during dosing.

different from the person conducting the physical examinations and assessing safety because the observation of stomal swelling, known to occur in relation to GLP-2 and teduglutide treatment, may have unblinded the observer.[22] The mode of parenteral adjustments, either by adjusting daily parenteral provisions or providing days off parenteral support, was entrusted to this person and was not specified in the protocol. As previously described, interim safety evaluations were performed within the week following adjustment to parenteral volumes. This was done by repeating 48 h urine collections, attaining weights and by reviewing the recorded oral fluid intakes as per the previous balance studies leading to a change in parenteral support in the algorithm. Blood samples were taken (including haematocrit, creatinine, blood urea nitrogen), urine sodium was measured and a clinical evaluation was performed checking for clinical signs of dehydration. Only if this assessment led to a conclusion that the new parenteral volume was tolerated would the weekly parenteral support volume be maintained until the next visit. Otherwise, the original parenteral volume was resumed.

The primary efficacy variable in the study was initially the responder rate—that is, the percentage of patients who had a reduction from baseline in parenteral volume of ≥20% at week 20 of treatment and again at week 24. A decrease of at least 20% in parenteral fluid was considered to result in a clinical benefit to the patients. After an independent review of the protocol by a statistical and regulatory panel prior to database lock, an expanded graded primary end point was introduced to compare the patients treated with teduglutide versus placebo with respect to a graded response score (GRS) criterion that accounted for both intensity and duration of a response at the end of the 24-week period. The intensity of the response relied on a reduction from baseline in weekly parenteral volume (from 20% to 100%). The duration of the response considered the responses at weeks 16 and 20, as well as weeks 20 and 24. The analysis of this expanded end point took into account higher levels of response and earlier onset of response coupled with a longer duration of response as shown in table 1. Thus, the score arose from the concept that, optimally, a graded change could be seen at the earlier time point and still observed at the later time point.

The statistical analysis of the GRS score compared the effects of placebo and teduglutide, starting with the 0.10 mg/kg/day dose according to a pre-specified step-down procedure.

Secondary efficacy end points included the number and percentage of subjects who responded (defined as a parenteral volume reduction of ≥20% from baseline at week 20 and maintained at week 24); the absolute reduction from baseline in parenteral volume and parenteral kilojoules; achievement of at least one day reduction in weekly parenteral administration or

Table 1 Criterion values for the graded response score

		Week 20 maintained at week 24			
		<20% reduction in PV	20–39% reduction in PV	40–99% reduction in PV	100% reduction in PV
Week 16 maintained to week 20	<20% reduction in PV	0	1	2	3
	20–39% reduction in PV	0	2	3	4
	>40% reduction in PV	0	3	4	5

total weaning from parenteral support. Further exploratory end points included the change from baseline in oral fluid intake and urine production, body composition (evaluated by DEXA),[22] plasma citrulline (an amino acid produced by enterocytes as a biomarker of a reduced enterocyte mass),[23] bowel morphology (histopathological evaluation and villus height and crypt depth morphometrics, optionally taken via stomas or by colonoscopy)[22] and health-related quality of life questionnaires (SF-36,[24] the EuroQol EQ-5D[25] and the IBDQ[26]).

Safety evaluations were conducted throughout the study, which included all reports of adverse events (AEs) and clinical laboratory tests. An independent data and safety monitoring committee oversaw the study.

All patients completing the randomised 24-week placebo-controlled trial were offered active treatment in a 28-week extension trial. The results from this study will be presented in a separate publication.

Statistical analysis

Based on the previous findings in a phase 2 study,[22] the prospective primary hypothesis was that subcutaneous injections of teduglutide would result in a higher GRS than placebo in patients with SBS dependent on parenteral support. The statistical analysis plan specified a step-down procedure which required teduglutide at a dose of 0.10 mg/kg/day to be statistically significantly greater than placebo before evaluation of the 0.05 mg/kg/day dose. Statistical analyses were performed on the intent-to-treat population. The analysis of AEs included all 83 patients who received at least one dose of the assigned treatment. Results are expressed as mean±SD.

All statistical tests were two-sided with an α level of 0.05. A sample size of 80 randomised subjects (32 subjects in each of the two teduglutide treatment groups and 16 subjects in the placebo group) was required to provide at least 90% power to detect an increase in the percentage of subjects who had the protocol-defined minimum response defined as a parenteral volume decrease of ≥20% for week 20 and maintained at week 24 which, on average, was estimated to correspond to one day off parenteral support (from 5% in the placebo treatment group to 50% in the teduglutide treatment groups in the study). The power calculations were based on two-sided tests of significance using the Fisher exact test.

For the analysis of the primary efficacy end point (the GRS), pairwise treatment comparisons were made using a rank analysis of covariance (an extension of the Wilcoxon rank sum test) with strata for the baseline parenteral consumption level used for the stratification of the randomisation and treatment groups, with the baseline weekly parenteral volume as a covariate and a step-down procedure for multiple comparisons. For the main secondary end point (responses maintained from week 20 and week 24 and defined as a ≥20% reduction from baseline in weekly parenteral volume), pairwise comparisons between treatment groups were made using the Fisher exact test.

RESULTS

Patients

In the period from May 2004 to November 2007, 139 patients signed informed consent forms and were screened at 32 centres in the USA, Canada, Denmark, France, Poland, Germany, the Netherlands, the UK and Belgium. Eighty-four patients with SBS were randomised and 83 were dosed (figure 1). The study NPS Pharmaceuticals in collaboration with the principal investigators on the writing team who had access to all data.

There were no significant differences in the demographic characteristics and medications among the groups at baseline compared with the placebo group, although parenteral volume and energy infusions tended to be higher in the 0.10 mg/kg/day teduglutide group (table 2). The numbers of patients completing the 24-week study were 15 (94%), 29 (88%) and 27 (77%) in the placebo, 0.10 mg/kg/day teduglutide and 0.05 mg/kg/day teduglutide groups, respectively.

Efficacy

Primary efficacy end point: GRS

The primary efficacy end point of the study, the GRS, was not significantly different from placebo in the teduglutide 0.10 mg/kg/day group (p=0.16), although a greater frequency of higher category responses was seen (table 3).

Ad hoc analysis of the primary efficacy end point

The prespecified statistical analysis plan required the 0.10 mg/kg/day dose to be significantly greater than placebo before further analyses. To gain further understanding about the effect of teduglutide, it was decided to explore the effect of the 0.05 mg/kg/day dose on the primary end point. These results showed a statistically significant improvement compared with placebo in the GRS for the 0.05 mg/kg/day teduglutide dose group (p=0.007).

Secondary and exploratory efficacy end points

The binary response end point represented the proportion of patients that responded to treatment which was defined as the achievement of a ≥20% reduction from baseline in weekly parenteral volume at week 20 and maintained at week 24. The responder rate was not significantly different between the teduglutide 0.10 mg/kg/day dose group and the placebo group (25% (8/32) vs 6% (1/16), p=0.17), but the responder rate was significantly higher in the teduglutide 0.05 mg/kg/day dose group compared with placebo (46% (16/35) vs 6% (1/16), p=0.005).

Three subjects were completely weaned from parenteral support; two patients in the 0.05 mg/kg/day teduglutide treatment group became completely independent of parenteral support after 25 and 6.5 years on this treatment, receiving 5.4 l and 3.5 l parenteral support per week at baseline, respectively. Another patient receiving the 0.10 mg/kg/day teduglutide dose, who had been receiving parenteral support for 3.7 years and received 4.5 l parenteral support at baseline, was also completely weaned from parenteral support at the end of treatment at week 24. Neither active treatment arm resulted in a significant reduction in the number of days on parenteral support.

As shown in figure 3, a minor but statistically significant reduction in parenteral volume was observed in patients in the placebo group at weeks 12 and 24 compared with baseline (106±167 ml/day, p=0.02 and 128±202 ml/day, p=0.03, respectively). No significant changes were seen in the oral fluid intake or urine volume in the placebo group.

Despite not meeting the a priori end point of a minimum reduction of 20% in parenteral fluid volume at weeks 20 and 24, patients receiving the teduglutide 0.10 mg/kg/day dose reduced their oral fluid intake by 342±599, 250±624, 365±575, 307±525, 359±638 and 392±647 ml/day at weeks 4, 8, 12, 16, 20 and 24, respectively, compared with baseline (all p<0.05). Oral fluid intake was significantly lower than placebo at weeks

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